Patentability Arguments:

The Examiner has questioned Applicants' reliance on Farooqi *et al.*, and Heymsfield *et al.* Applicants realize that both Farooqi *et al.*, and Heymsfield *et al.*, used protein therapy. However, the Examiner's contention that "the relevance of these teachings to the rejection regarding enablement of gene therapy claims is not clear" ignores the fact that these references directly speak to knowledge in the art of how to identify individuals who will benefit from or respond to OB therapy intervention, be it in the form of protein administration or a gene therapy protocol. The references also indicated that the administration of OB, in fact, results in the modulation of body weight. Farooqi *et al.*, 1999 and Heymsfield *et al.*, 1999 unequivocally demonstrated that the animal model data presented in the instant specification regarding OB administration correlates to human treatments.

Moreover, the Examiner appears willing to admit that *OB* gene therapy in *ob/ob* mice is effective as supported by Fletcher *et al.* (1995), Fletcher *et al.* (1996) and Muzzin *et al.* (1996) which references present studies demonstrating the efficacy of *OB* gene therapy *in vivo* in such animals. Fletcher et al., (1996) also demonstrated the efficacy of *OB* gene therapy in wild-type mice. Each of these references used a different vector to achieve the therapeutic effect. Nevertheless, the Examiner wrongly maintains that it is irrelevant whether these studies have demonstrated gene therapy in mice because these "references are not commensurate with the scope of the claimed invention and do not illustrate enablement of the full scope of the instant claims." Evidently, it is the Examiner's position that because the claimed invention is directed to human gene therapy, then any indications provided from mouse studies are irrelevant. This position is in direct contradiction to established law and the USPTO's previous decisions and is therefore untenable.

The MPEP clearly takes the position that an "*in vivo* animal model example in the specification, in effect, constitutes a 'working example' if . . . [the] particular model is recognized as correlating to a specific condition . . . unless the Examiner has evidence that the model does not correlate" MPEP 2164.02. Furthermore, the MPEP states that even if there is evidence that an animal model is not an exact match for the human condition, such evidence for and against correlation must be weighed to decide whether one skilled in the art would accept the model as reasonably correlating to the condition in humans. *Id.* citing *In re* Brana, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995).

Data obtained from animal studies has long been recognized to be indicative of human utility. *In re* Hartrop, 135 U.S.P.Q. 419 (CCPA 1962). At this point it is beyond doubt that data from mice are predictive of utility in humans. See *In re* Bergel and Stock, 130

U.S.P.Q. 206, 209 (CCPA 1961); *In re* Ross and Davis, 134 U.S.P.Q. 321 (CCPA 1962), citing Bergel; *Ex parte* Westphal and Damagk, 139 U.S.P.Q. 378 (POBA 1962). Furthermore, even if the Examiner maintains the stance that environmental conditions play a larger role in human obesity than animal model obesity, Applicants refer the Examiner to MPEP 2164.02 which instructs that "a rigorous or an invariable exact correlation is not required." As such, and as a matter of law, the evidence from animal model data provided by the Applicants is sufficient to enable the scope of the claims and the Examiner has provided no objective evidence that animal model studies do not correlate to efficacy of *OB* gene therapy in humans.

Given that the protein animal model data from the instant application have been duplicated by Farooqi *et al.* and Heymsfield *et al.*, and further given that Fletcher *et al.*, (1995), Fletcher *et al.* (1996) and Muzzin *et al.*, (1996) have demonstrated the efficacy of gene therapy using different OB encoding vectors, there is no reason to believe that the results of *OB*-based gene therapy intervention in mammals will not correlate to human treatments. The Examiner nevertheless generally states that *OB*-based gene therapy will not work because gene therapy is unpredictable.

The Examiner's position ignores the fact the USPTO routinely issues U.S. patents directed to gene therapy. The Examiner dismisses the list of gene therapy patents cited by the Applicants stating that each application is judged individually on its merits and it is not significant that other patents have been allowed claiming gene therapeutic applications. While it is acknowledged that each specification is required to be individually enabling, Applicants maintain that the patents cited by the Applicants in their previous response objectively show that gene therapy is widely applicable across the board for a wide variety of diseases and disorders. The Examiner's position ignores this point and provides no ***objective reasoning*** why gene therapy is too unpredictable for modifying the body weight of a mammal despite its demonstrated success in animal models.

Contrary to the Examiner's assertion that the instant application does not provide enablement for the claims, Applicants maintain that the specification is a roadmap for how one of skill in the art would modify the body weight of a mammal by administering to the mammal a vector comprising a nucleic acid molecule encoding an OB polypeptide that is capable of modulating body weight under conditions that provide for expression of the OB polypeptide *in vivo*. To this end, the present application discloses vectors and compositions for use in gene therapy applications. For example, the Specification at page 83, line 16 through page 85, line 10 specifically discusses that gene therapy into human cells would be

expected to modulate (decrease or increase) body weight. This section provides exemplary methods of introducing the *OB* gene *in vivo* using, for example, various viral vectors including adenoviruses, retroviruses, adeno-associated viruses as well as others. Such vectors were well known to those of skill in the art in 1994, and given the teaching of the present application, one of skill in the art would have been able to employ such vectors in the gene therapeutic applications of the present invention without undue experimentation. In addition to the gene sequences of wild-type mouse and human *OB* gene, the present application further describes additional variants and analogs of these genes for use in gene therapy applications.

With respect to the Examiner's recitation of the Forman factors, Applicants maintain that the instant disclosure and the level of skill in the art is such that gene therapy is ***not*** unpredictable and would not require undue experimentation. Firstly, Applicants disagree with the Examiner's inaccurate characterization of the instant invention as a "hunting license". The specification provides detailed disclosure of gene sequences, vector components and delivery methods to achieve *in vivo OB* gene delivery and expression. Applicants have also provided evidence that these methods are effective in modulating body weight in art-recognized animal models of obesity. The Examiner has failed to provide anything other than a generalization about the unpredictability of gene therapy to rebut this objective evidence.

In previous responses, Applicants have provided specific examples of areas in which gene therapy has been shown to be successful. Thus, while there may be obstacles in gene therapy methods, such obstacles are not insurmountable and are navigable by those of skill in the art given that the instant application provides details of the gene sequences and vectors that can be used in such protocols in modulating body weight *in vivo*. Contrary to the Examiner's assertion that the application does not provide details of how to identify individuals in need of such therapy, Applicants have provided details of different assays that may be used in diagnostic methods. In the previous response, under the heading "Identification of those Individuals Who May Benefit from Treatment" Applicants provided details of where in the specification and in the art one of skill in the art may find guidance to identify those individuals that could reasonably be expected to benefit from the administration of the *OB* gene (or polypeptide) to modify body weight. The Examiner dismissed this teaching as "merely a generalized description" rather than specific protocols. A specification is intended to teach one of skill in the art how to make and use the invention, it need not be a manual of instructions containing specific recipes for particular protocols. The test for enablement is "whether a person of ordinary skill in the relevant art, using his or her knowledge and the

patent disclosure, could make and use the invention without undue experimentation." *Williams Service Group Inc. v. O.B. Cannon & Son Inc.*, 33 USPQ 2d 1705, 1723 (Pa. 1994).

Heymsfield *et al.* demonstrate that identifying individuals responsive to OB therapy does not require undue experimentation (Heymsfield *et al.*, JAMA Vol. 282 No. 16, 1568-75, 1999). As can be seen from the abstract, in a completely ***randomized*** trial in which 54 lean and 73 obese men and women were treated with OB, weight loss was seen in both lean and obese individuals. Thus, far from the examiner's assertions, Heymsfield *et al.* objectively demonstrates that one of skill in the art will readily be able to identify individuals who could benefit from the methods of the present invention without using undue experimentation.

Ultimately, the Examiner maintains that given that the nature of gene therapy is unpredictable, the amount of experimentation that is required would be undue. This position cannot be maintained in light of Applicants' teachings and the level of skill in the art. The fundamental tenet of enablement is not that experimentation is required, but rather that the experimentation not be ***undue***. *In re Wands*, 8 USPQ2d 1400, 1404. Indeed, it may well be that additional experimentation is needed to perfect the gene therapy protocols, however, Applicants maintain that in light of the present disclosure, one of skill in the art would readily be able to conduct such protocols to achieve a modulation of body weight of a mammal because ***the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.*** *Id.*

In light of the above comments, Applicants believe the instant case is in condition for allowance and respectfully request such a favorable reconsideration.

Respectfully submitted,

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